



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 7/48	A1	(11) International Publication Number: WO 98/17246 (43) International Publication Date: 30 April 1998 (30.04.98)
<p>(21) International Application Number: PCT/IB97/01318</p> <p>(22) International Filing Date: 21 October 1997 (21.10.97)</p> <p>(30) Priority Data: 96/12821 22 October 1996 (22.10.96) FR</p> <p>(71) Applicant (for all designated States except US): ROC [FR/FR]; 48/50, rue de Seine, F-92700 Colombes (FR).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): CASTELLI, Dominique [FR/FR]; 12, rue Poncelet, F-75017 Paris (FR). RIES, Gerd [DE/DE]; Johnson & Johnson, Kaiserswerther Strasse 270, D-40474 Düsseldorf (DE). FRITEAU, Laurence [FR/FR]; 60, rue de Ecoles, F-94000 Cretail (FR). BOUSIGNIERE, Elisabeth [FR/FR]; 6, rue du Général Roguet, F-92100 Clichy (FR). FREDON, Laurent [FR/FR]; 18, avenue de la République, F-92400 Courbevoie (FR).</p> <p>(74) Agents: MARTIN, Jean-Jacques et al.; Cabinet Regimbeau, 26, avenue Kléber, F-75116 Paris (FR).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: USE OF COMPLEXES FOR THE PREPARATION OF COMPOSITIONS FOR THE TREATMENT OF SENSITIVE SKIN, PREPARATION PROCESS AND HYPOALLERGENIC COMPOSITIONS</p>		
<p>(57) Abstract</p> <p>The present invention relates to the use of at least two compounds chosen from components having an a) anti-radical, b) anti-inflammatory and c) anti-allergic activity for the preparation of a composition exhibiting at least two of the a), b) and c) activities intended for the treatment of sensitive and/or allergic skin. It also relates to a process for the preparation of such compositions and to the compositions thus obtained.</p>		

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USE OF COMPLEXES FOR THE PREPARATION OF COMPOSITIONS FOR
THE TREATMENT OF SENSITIVE SKIN, PREPARATION PROCESS AND
HYPOALLERGENIC COMPOSITIONS

5 The invention relates to new dermocosmetic and
pharmaceutical compositions which are useful for improv-
ing and treating hyperreactive skin conditions and more
generally allergic-type reactions and/or intolerance
phenomena, whether they are caused by external factors or
factors intrinsic to the individual.

10 Increasing numbers of children and adults are in
fact exhibiting skin described as "sensitive". During a
recent study in France, 70% of the women questioned
stated that they had sensitive facial skin. The notion of
sensitive skin covers an array of outward signs
15 comprising reactive skin and intolerant skin. Atopic skin
can also be included therein. These skin types are
sometimes incorrectly known as "allergic" by the sub-
jects; however, while an allergic component can sometimes
be evoked in the symptoms of sensitive skin, it may not
20 be restricted to it. The triggering factors can be
environmental attacks such as wind, pollution, tem-
perature variations, excessively hard water or ill-suited
hygiene, cosmetic or care products; these phenomena can
also be associated with stress or emotions felt by the
25 subject, some diets or the taking of medicaments. In
addition, there exists individual predisposing factors
(in particular neurological or hormonal) or familial
predisposing factors which amplify these reactions.

Generally, the subject feels cutaneous discomfort
30 which can manifest itself by subjective and/or objective
signs. The skin readily gives off stabbing pains, itches
or smarts and the subject may experience feelings of
warmth, pricking or burning on the skin. The skin can
redden or desquamate. Xerosis, seborrhoeic dermatitis,
35 telangiectasias, vesicles or even oedema is observed, on
an irregular basis.

In the most serious cases, dermatological com-
plaints of immunoallergic type, such as atopy, eczema or
neurodermatitides, may be observed.

- 2 -

This condition can manifest itself on the skin, the mucous membranes or the scalp. In the latter case, it may be associated with a dandruff condition and/or alopecia.

5 Until now, attempts have been made to prevent the appearance of these reactions by limiting the presence, in dermocosmetological formulations, of components known to be allergizing. However, it would be desirable to be able to have available truly active compositions which
10 are capable of preventing or of relieving these symptoms by decreasing the reactivity of the skin and by improving its resistance to the triggering factors.

 The Applicant Company has now found, unexpectedly, that these aims could be achieved by the use of
15 a composition containing a synergic combination producing an active hypoallergenic complex.

 Such a complex will, in addition, improve the receptivity of the skin towards other active principles.

 For this reason, the subject of the present
20 invention is a dermocosmetic composition, characterized in that it contains an immunomodulatory or hypoallergenic synergic combination of at least two components, each of these components exhibiting at least one of the following activities:

- 25 a) anti-radical
 b) anti-inflammatory
 c) anti-allergic.

the said components being chosen so that at least two activities a), b) or c) are present in the composition.

30 The subject of the invention is more particularly the use of at least two compounds chosen from components having an a) anti-radical, b) anti-inflammatory and c) anti-allergic activity for the preparation of a composition, in particular an immunomodulatory composition,
35 exhibiting at least two of the a), b) and c) activities intended for the treatment of sensitive and/or allergic skin; according to one of its aspects, the a), b) and c) activities are exerted in the composition.

 Indeed, the Applicant Company has been able to

- 3 -

show that the combination of active principles having complementary anti-allergic, anti-radical and/or anti-inflammatory activities made it possible to effectively combat the phenomena associated with the appearance of the symptoms of sensitive and/or intolerant skin or of immunoallergic complaints, preferably via a synergy of the activities of the components.

The components forming part of the formulations according to the invention can be purified or unpurified molecules, synthetic or extracted products, mixtures of active principles or extracts which have been subjected to one or a number of fractionation stages from a starting material of plant or animal origin.

Preferably, if two components present in the formulation show an activity of the same type, it will be exerted by the involvement of a different mechanism.

As regards the anti-inflammatory activity, it can in particular be provided by prostaglandin inhibitors (cyclooxygenase route), inhibitors of cytokine production and inhibitors of the production of leukotrienes (LTB₄, for example, lipoxxygenase route).

The component or components with anti-inflammatory activity advantageously exhibit an inhibiting activity on the production of IL-1, IL-2, IL-4, IL-6, IL-12 and/or TNF- α (Tumour Necrosis Factor).

The anti-inflammatory function can also have the consequence of decreasing the production of reactive nitro derivatives by the cells, limiting the generation of free radicals.

However, anti-radical activity is understood to mean components which are preferably chosen from free-radical scavengers, anti-lipoperoxidants and stimulants of the endogenous production of the enzymes which degrade free radicals.

Free radicals, by definition, are neutral or charged chemical species which have an unpaired electron. This "single electron" endows them with specific chemical properties and a short lifetime. They are reaction intermediates which will be stabilized by combination or

transfer and can be the source of a chain reaction. Mention may be made, among free radicals, of the superoxide anion $O_2^{\cdot -}$, the hydroxyl radical OH^{\cdot} , NO^{\cdot} or peroxides.

5 Enzymes which are active in endogenous defence systems against free radicals are, for example, SOD (or superoxide dismutase), catalase or glutathione peroxidase; attempts will be made to stimulate the production of these enzymes or they can be introduced
10 exogenously.

 The components providing the anti-allergic function in the composition according to the invention are preferably chosen from inhibitors of lymphocyte proliferation, inhibitors of the internalization of the
15 molecules of the major histocompatibility complex (HLA-DR, for example) or inhibitors of cytokine production. They are advantageously capable of decreasing the production of the mediators of the inflammation which occurs during allergic phenomena.

20 As indicated above, the composition will exhibit at least two of the anti-radical, anti-inflammatory and anti-allergic activities. In addition, the components of the active hypoallergenic complex will be chosen so that a synergy is exerted via different mechanisms at the
25 basis of the same activity.

 Each component will preferably contribute, via a number of parameters, to the overall activity of the composition according to the invention.

 The composition according to the invention
30 advantageously has a marked inhibiting activity on the synthesis and/or the expression of neuromediators, in particular with respect to cutaneous cells, resulting from a synergy of the activities of its different components. The neuromediators can be chosen from the
35 group comprising neurokinines A (NKA) and B (NKB), vasoactive intestinal polypeptide (VIP), calcitonin gene related peptide (CGRP), neuropeptide Y (NPY), neurotensin (NT), somatostatin (SOM), gastrin releasing peptide (GRP), nerve growth factor (NGF), PGP 9.5 (Protein Gene

- 5 -

Product 9.5) and bombesin.

Components making possible the preparation of dermocosmetic compositions according to the invention can advantageously be chosen from the following group: Ginkgo
5 biloba and its extracts, iramine, D-panthenol, β -sitosterol, modulene, α -tocopherol and its derivatives, β -glucan and its derivatives, eicosapentanoic acid, 18 β -glycyrrhetinic acid, glycyrrhetinic acid monoglucuronide, stearyl glycyrrhetinate, Scutellaria extract,
10 lactoferrin, green tea and its extracts, vitamin C, glutathione, epidermal thymus factor, azole derivatives and lipacid.

However, the combination of vitamin E with a Scutellaria extract is not included within the compositions according to the invention.
15

According to one of the aspects of the invention, the composition contains at least one component, preferably at least two components, chosen from the above group.

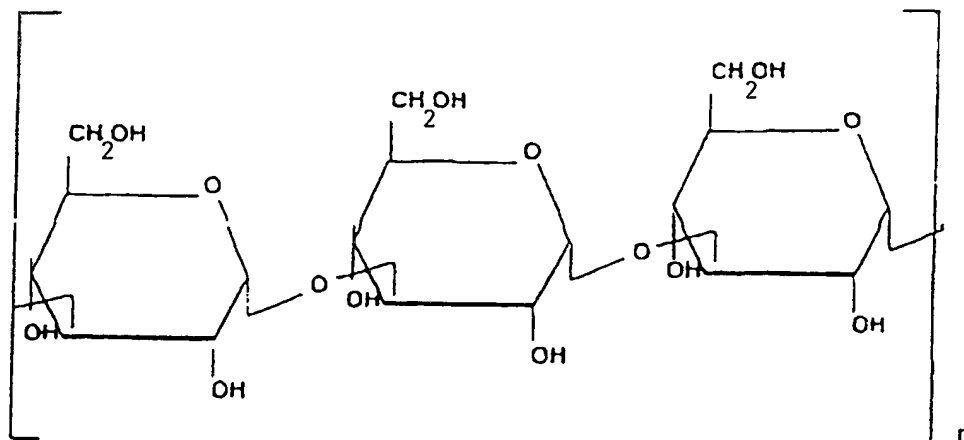
20 The azole derivatives used according to the invention can be chosen from imidazole or triazole derivatives and in particular from the group composed of: bifonazole, butoconazole, chlordanol, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole,
25 lanconazole, miconazole, omiconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, itraconazole, saperconazole, terconazole or elubiol.

This is because it has now been possible to demonstrate that these compounds exhibit in particular an anti-radical activity.
30

Mention may more particularly be made, among α -tocopherol derivatives which can be used, of α -tocopherol phosphate.

35 Mention may be made, among β -glucan derivatives, of carboxymethyl- β -glucan and drieline[®].

Drieline is a poly- β (1 \rightarrow 3)-glucopyranose of formula



$n = 1000$

with $n = 1000$.

The molecule can be provided in the form of a 0.1% solution in water and sorbitol or in the powder form.

5 In one of the preferred embodiments of the invention, the composition contains a synergic combination of a Ginkgo biloba extract and of a β -glucan compound.

10 Indeed, the Applicant Company has found that the combination of these two components made it possible to obtain the optimum combination of the functional characteristics providing the activity of the compositions according to the invention.

15 The glucan is composed of a $\beta(1\rightarrow3)$ glucose chain which can in particular be extracted from the wall of yeast cells. It is possible to subject it to chemical modifications in order in particular to improve its solubility.

20 The β -glucan is advantageously substituted by carboxymethyl groups; it can exist in the salt form, in particular the sodium salt form. Good results are obtained with a derivative in which the degree of substitution by carboxymethyl groups is within the range from 0.65 to 0.85 and which exhibits a pH from 5.5 to 8.5.

25 Ginkgo biloba is a dioecious tree from the Far East, the leaves of which are used for certain medicinal properties. They contain constituents, such as aliphatic hydrocarbons and alcohols, polyphenols, such as luteolin

- 7 -

or quercetol, or biflavones derived from amentoflavone, and more specific constituents: ginkgolic acid, and anacardic derivatives, terpenes derived from limonene or terpenes containing a tert-butyl group.

5 Ginkgo extracts have been proposed for improving the symptoms of mental deficiency in the elderly, of intermittent claudication, of obliterating chronic arteriopathies and of Raynaud's disease, or in the case of retinal deficiency.

10 They have been used in cosmetology for their protective effect with respect to free radicals.

 The Applicant Company has found, unexpectedly, that ginkgo extracts have an excellent anti-inflammatory and anti-allergic activity which can be demonstrated on
15 cutaneous cells, such as keratinocytes and macrophages. In addition, the Applicant Company has shown that this activity is potentiated in the presence of β -glucan.

 Extracts which are particularly suitable for the implementation of the invention are obtained from Ginkgo
20 biloba leaves which have been subjected to a stage during which the terpene concentration has been brought to a value of less than approximately 7% and preferably of less than approximately 3% (w/w of dry extract). In one of the embodiments, this terpene concentration is less
25 than approximately 1% w/w.

 The concentration of flavone heterosides in the dry extract is advantageously greater than 24% and preferably greater than approximately 26% w/w.

 The anti-inflammatory and anti-allergic prop-
30 erties can be demonstrated in particular with respect to in vitro models, for which a correlation exists with animal models and clinical studies already carried out on man.

 It is possible in particular to operate on
35 keratinocytes and macrophage cells because these are cells which are essential for the development of a local inflammatory reaction. Moreover, macrophages are particularly advantageous cells because, due to the fact that these are resident cells in the skin, they regulate not

only local inflammatory reactions but they also regulate the immune responses by their ability to present the antigen and to produce a great number of cytokines which regulate local immunity. These macrophages are also
5 involved in communications with the circulatory system which can, if appropriate, mobilize different cell types (monocytes, neutrophils, eosinophils and T lymphocytes), thus increasing the non-specific and specific defensive power of the tissue under consideration.

10 The activities of the test products are therefore investigated with respect to human macrophage and keratinocyte cultures which are or are not stimulated by interferon- γ + lipopolysaccharide (non-specific inflammation) or by IL-4 (allergic inflammation). This
15 type of stimulation places the cells in the context of a pro-oxidizing response (generation of NO or superoxide anion free radicals, which can be evaluated by measuring the production of nitrogenous derivatives) and an immunoinflammatory response (production of cytokines such as
20 TNF- α).

To evaluate the allergic inflammation, the cells are activated by IL-4, which induces the CD23 receptor, and then by IgE-containing immune complexes. In all cases, the cellular supernatants are analysed after the
25 activation.

A viability study is in addition carried out on the cells.

The activity of the components is also confirmed on mixed lympho-epidermal cultures (MLEC).

30 In the skin, Langerhans cells indeed play an essential role in the presence of the antigen and keratinocytes generate factors which are involved in the immune response, thus constituting a cutaneous immune system. MLECs make it possible to determine the immunomodulatory properties of substances by measuring the
35 lymphocyte proliferation induced by the antigen-presenting allogenic epidermal cells, with or without treatment by the substance.

The results obtained with ginkgo and β -glucan are

summarized in the table below:

Activity	Mediator or parameter	Ginkgo biloba	β -Glucan
5 Anti-inflammatory	· LTB ₄	inhibition	no effect
	· PGE ₂	no effect	inhibition
	· IL-1 α	no effect	inhibition
	· TNF- α	no effect	inhibition
Anti-free radicals	· peroxidation of the lipids	inhibition	no effect
	· NO	inhibition	inhibition
	· catalase	no effect	stimulation
	· glutathione peroxidase	stimulation	stimulation
Anti-allergic	· MLEC	inhibition	no effect

10 Compositions according to the invention contain in particular from 0.001% to 10% w/w of a ginkgo extract and preferably from 0.05 to 2%; according to one of the embodiments, the concentration of ginkgo extract will be from approximately 0.1 to 0.5% but it will be adjusted by
15 the person skilled in the art.

Concentrations of β -glucan, in particular carboxymethylated β -glucan, which are suitable for the implementation of the invention are within the range from 0.001% to 10% w/total w of the composition.

20 Other compositions which are particularly suitable for the invention comprise the combination of lactoferrin and drieline, panthenol and green tea extract or panthenol and β -sitosterol. A combination of α -tocopherol (or one of its salts) and a ginkgo extract can
25 also be used according to the invention. Such combinations produce an active hypoallergenic complex which lowers the reactivity threshold of the skin and of the scalp and decreases the magnitude of the possible intol-

- 10 -

erance or immunoallergic reactions.

The green tea extract is obtained from dry *Camellia oleifera* leaves and contains, in particular, theophylline, caffeine and theobromine.

5 Another subject of the invention is a process for the preparation of an active hypoallergenic complex, characterized in that substances belonging to at least one of the groups: anti-free radical, anti-inflammatory and immunomodulatory active principle are selected and in
10 that two substances having complementary activities are then combined so as to potentiate the anti-radical, anti-inflammatory and anti-allergic functions of the combination.

The combination of the substances constituting
15 the active hypoallergenic complex preferably decreases the synthesis or the expression of the neuromediators, such as VIP, PGP 9.5 or CGRP, which are correlated with so-called "sensitive" or irritable skin.

Another subject of the invention is a method for
20 the cosmetic treatment of sensitive skin comprising the application to the skin of the body or of the face, one or a number of times per day, of active hypoallergenic complexes and/or compositions as defined above.

In particular, the invention relates to a method
25 for the treatment of alopecia which comprises the weekly, twice-weekly, daily or twice-daily application to the scalp of a combination of anti-radical, anti-inflammatory and/or anti-allergic components. The combinations can be in different formulations, such as shampoos or lotions,
30 which can be applied simultaneously, separately or sequentially, optionally with other active principles which are active with respect to alopecia, dandruff conditions and/or seborrheic conditions.

Another of the subjects of the invention is the
35 use of a hypoallergenic complex as defined above for the preparation of an immunomodulatory medicament, in particular intended for the treatment of a complaint chosen from atopy, psoriasis, erythema multiforme, xerodermatitides, lupus erythematosus, pemphigus, dermatitides,

rosacea, acne, eczemas and neurodermatitides.

The hypoallergenic combinations according to the invention will advantageously be formulated within compositions also containing moisturizing agents and/or agents which improve cutaneous penetration, which will promote the activity of the complex according to the invention. Mention may be made, by way of examples, of urea, propylene glycol or oleic acid, the person skilled in the art being capable of using other penetration promoters suited to the type of formulation.

The compositions according to the invention will in addition contain pharmaceutically and/or cosmetologically acceptable excipients known to the person skilled in the art suited to their formulation, in particular in the form of solutions, lotions, creams, shampoos, emulsions, and the like.

Mention may be made, in a non-limiting way, of pigments, dyes, preservatives, texturing agents, thickeners, emulsifiers or fragrances. They can also contain sunscreens agents or blockers or another active principle.

Finally, the hypoallergenic complexes containing the combinations according to the invention can be introduced into compositions containing at least one active principle by the topical route, in particular when this active principle is capable of causing a cutaneous reaction.

Mention may more particularly be made, among such active principles, of retinoids and depigmenting active agents.

Retinoids is understood to mean in particular retinoic acid or tretinoin, retinol, retinaldehydes, their salts and their esters. The alkali metal, ammonium and C₂-C₃₀ ammonium salts are typical salts. The sodium, potassium, triethanolammonium and ammonium salts are particularly preferred. The combinations of all the above compounds can be present in the compositions. In addition, the terms "retinol" and "retinoic acid" must be understood as including the hydrogenated and non-

- 12 -

hydrogenated isomers, such as 9-cis-retinol, didehydro-retinol, 13-cis-retinoic acid, 13-trans-retinoic acid and didehydroretinoic acid.

The depigmenting agents comprise, for example,
5 kojic acid, hydroquinone, vitamin C, vitamin C magnesium phosphate, carotenoids, arbutin, and the like.

The following examples are intended to illustrate the invention.

In these examples, reference will be made to the
10 following figures:

Figure 1: Dose effect of carboxymethyl- β -glucan with respect to the inflammatory functions of the keratinocytes.

Figure 2: Synergy between a Ginkgo biloba extract (H37)
15 and carboxymethyl- β -glucan (K18) in their anti-inflammatory functions with respect to keratinocytes.

Example 1

1. Materials and Methods

20 Products

The following products were used during this study: Escherichia coli LPS (Sigma), used at 1 μ g/ml. IFN- γ and IL-4 are sourced from Immugenex (Los Angeles CA) and are used respectively at 1000 U/ml and 10 ng/ml,
25 the monoclonal IgEs are sourced from Stallergène (Fresnes, France) and the anti-IgEs are from Nordic (Tilburg, Holland).

Keratinocyte culture

The keratinocyte primary cultures are obtained
30 from neonatal foreskins and are maintained in proliferation *ex vivo* in a medium which does not contain calf serum. The confluent keratinocyte cultures are trypsinized and transferred into 24-well plates in fresh medium at the cellular density of 10^5 cells/ml/well. If
35 appropriate, in the case of stimulation by IL-4, the presence of the IgE receptor (CD23) at the surface of the

- 13 -

cells is verified by immunolabelling.

Macrophage culture

The macrophage cells are obtained from the peripheral blood of normal donors (non-allergic). The mononuclear cells are isolated on a ficoll gradient and the ring of lymphoid cells is recovered and washed three times and the cells are then cultured so as to cause the macrophage cells to adhere. These cells are recovered after adhering for 1 hour and are cultured (10^6 cells/ml/well). If appropriate, in the case of stimulation by IL-4, the presence of the IgE receptor (CD23) at the surface of the cells is verified by immunolabelling.

Cell activation

The cells are activated by the combination of IFN- γ and LPS for 3 to 4 days and the supernatants of these cultures are then recovered in order to quantitatively determine the nitrogenous derivatives and TNF- α . Likewise, during stimulation by IgE, the cells are first activated by IL-4, so as to induce the CD23, and are then subsequently cultured and stimulated by the IgE-containing immune complexes for 3 to 5 days before recovering the different supernatants. In all the cases, cellular viability is achieved on conclusion of these cultures. In the specific case of macrophages, a long-term (7 to 12 days) viability study was carried out, so as to determine the protective effects of these products. Quantitative determination of the nitrogenous derivatives is carried out using the Griess approach and the TNF level is measured by using quantitative determination kits from Medgénix (Fleurus, Belgium).

2. Results

2.1. Effect of a Ginkgo biloba extract on the keratinocytes and the macrophages stimulated by IFN- γ + LPS

Dry Ginkgo biloba leaves were subjected to continuous extraction by an acetone/water mixture under vacuum and then several stages of removal of solvent as well as of chlorophyll, lipids, waxes, lectins and of certain substances result in an extract subsequently

denoted by H37.

It exists in the form of a fine powder corresponding to the following specifications:

- residual solvents		
5	• ethanol	< 3%
	• acetone	< 0.1%
	• butanol	< 0.1%
	• ethyl acetate	< 0.1%
	- sulphated ash	< 1.5%
10	- water content	< 3%
	- pro-anthocyanidins	< 5%
	- terpenes	< 0.5%
	- ginkgolic acid	< 10 ppm
	- heavy metals	< 20 ppm
15	- flavone heterosides	32 ± 3%

It is 6% (w/w) soluble in PEG 400 and 4% (w/v) soluble in 90° ethanol.

In this study, the product H37 (10 mg/ml) is added 30 min before stimulation by IFN- γ + LPS. This product showed no cytotoxic activity.

Table 1A : Production of nitro derivatives (NO_2^- μM) after stimulation by IFN- γ + LPS +/- 10 mg/ml H37

Cells		Expt-1	Expt-2	Expt-3	Expt-4
25	Macrophages	11(5)*	15(5)	5(3)	2(9)
	+H37	7(4)	8(4)	2(2)	2(2)
Keratinocytes		12(15)	17(3)	23(12)	13(5)
	+ H37	7(6)	7(3)	8(11)	6(4)

* The values between brackets are those of cells which have not been stimulated by IFN- γ + LPS

Table 1B : Production of TNF (pg/ml) after stimulation
by IFN- γ + LPS +/- 10 mg/ml H37,

Cells	Expt-1	Expt-2	Expt-3	Expt-4
Macrophages	755 (ND)*	1250 (155)	998 (55)	1510 (ND)
+H37	605 (ND)	1120 (75)	895 (50)	1315 (ND)
5 Keratinocytes	187 (ND)	173 (ND)	208 (ND)	135 (ND)
+ H37	168 (ND)	165 (ND)	112 (ND)	105 (ND)

* The values between brackets are those of cells which have not been stimulated by IFN- γ + LPS, ND = non-detectable.

Through these experiments, it appears that the
10 macrophages stimulated by IFN- γ + LPS do not produce
nitro derivatives to a significant extent whereas the
keratinocytes produce it reproducibly. In fact, it has
recently been demonstrated that, during such a
stimulation, the macrophages produce a truncated NO
15 synthase which could have a significant decrease in its
activity, which is apparently not the case for the
keratinocytes.

In the keratinocytes, H37 inhibits the production
of NO after stimulation.

20 The product H37 exhibits a slight "anti-
inflammatory" activity. Moreover, on evaluating the dose
effect of H37 on this production by the keratinocytes, it
is shown that the maximum effect is observed at 10 mg/ml.

In addition, H37 protects the macrophage cells
25 from the cell death induced by radical products. The fact
that the stimulated macrophages do not produce
significant amounts of nitro derivatives does not rule
out the fact that these cells are not subjected to an
oxidative shock which can result in cell death.

30 This is objectivized by comparisons of the
effects on the long-term cell viability at 10 days or
with the short-term cultures (2 days). It appears that

H37, at 10 mg/ml, protects the macrophage cells from the cell death induced most of the time by the radical products.

5 Table 2 : Effect of H37 on the viability of the macrophages

Macrophages + IFN/LPS	% of viable cells at D2	% of viable cells at D10
Medium	85 \pm 2	55 \pm 7
+ H37	88 \pm 3	80 \pm 2

10 2.2. Effect of the product H37 on the macrophages and the keratinocytes stimulated by IL-4.

The cells are stimulated for 48 h in the presence of IL-4 (10 ng/ml), so as to induce the receptor with a low affinity for the IgEs (CD23) at their surface. On
 15 completion of this culturing period, 30 to 80% of the keratinocytes and of the macrophages express CD23. The individual variations are in no case the reflection of a different allergic situation between these individuals. Whatever the situation, in this induction phase, the
 20 tested product does not modify this induction of CD23; in fact, a decrease of less than 5% cannot be observed (n=8).

25 Table 3 : Induction of the expression of CD23 by the different cells stimulated by IL-4 in the presence or in the absence of 10 mg/ml H37

Cells	Medium	+ IL-4
Macrophages	< 5%	45 +/- 4
+H37	< 5%	41 +/- 2
Keratinocytes	ND	55 +/- 7
30 +H37	ND	51 +/- 4

* The cells are stimulated for 48 h in the presence or in the absence of 10 ng/ml of IL-4 and in the presence or in

- 17 -

the absence of the different products, ND = non-detectable.

After the CD23 has been taken up by IgE-containing immune complexes, the production of a large number of mediators and cytokines (in particular TNF) and of products resulting from the oxidative metabolism, such as nitrogenous derivatives, is induced. This stimulation redefines in vitro an allergic-type inflammatory reaction.

In this case, the results observed are in every respect comparable with those obtained with IFN- γ and LPS, which tends to demonstrate that H37 exhibits certain anti-inflammatory activities (non-specific and allergic), probably via its ability to regulate the oxidizing abilities of the "inflamed" cells. The results obtained are summarized in the following two tables:

Table 4A : Production of nitro derivatives (NO_2^- μM) after stimulation by IL-4 +/- 10 mg/ml H37

Cells	Expt-1	Expt-2	Expt-3	Expt-4
Macrophages	25(5)*	30(2)	55(11)	15(2)
+H37	15(2)	17(75)	21(50)	6(2)
Keratinocytes	17(13)	13(3)	23(12)	13(5)
+ H37	12(11)	8(2)	10(10)	8(6)

* The values between brackets are those of cells which have not been stimulated by the IgE-containing immune complexes.

The product H37 exhibits a good ability to inhibit the production of nitro derivatives by the macrophages and the keratinocytes stimulated by IL-4.

Table 4B : Production of TNF (pg/ml) after stimulation
by IL-4 +/- 10 mg/ml H37

Cells	Expt-1	Expt-2	Expt-3	Expt-4
Macrophages	975 (105)	275 (35)	455 (40)	310 (89)
+H37	850 (105)	215 (25)	365 (35)	275 (87)
5 Keratinocytes	185 (ND)	158 (ND)	315 (35)	308 (ND)
+ H37	155 (ND)	120 (ND)	245 (30)	276 (ND)

The values between brackets are those of cells which have not been stimulated by the IgE-containing immune complexes, ND = non-detectable.

The product H37 induces a slight decrease in the production of TNF- α by the macrophages and the keratinocytes stimulated by IL-4.

Just as during the non-specific stimulation, it appears that H37 increases the long-term viability of the macrophages and of the keratinocytes stimulated by the IgE-containing immune complexes, which, again, suggests very strongly that the product H37 exerts its slight anti-inflammatory activity via an anti-oxidizing activity with respect to the target cells.

It therefore appears that the product H37 exhibits an anti-inflammatory activity (allergic or non-allergic). This characteristic is very important because the seriousness of the inflammatory responses, whether or not of allergic origin, results from an imbalance in the oxidative metabolism of these cells. It is in particular this imbalance which is the source, at least in part, of the regulation of the immunological phenomena associated with these reactions: this is the case for specific allergen reactions and for the production of cytokines.

2.3. Effect of the products K17 and K18 on the keratinocytes and the macrophages stimulated by IFN- γ + LPS

Drieline is denoted by K17. Drieline is a poly- β (1 \rightarrow 3)-glucopyranose purified from *Saccharomyces cerevisiae* yeast membranes; it is in solution in a

water/sorbitol mixture.

Carboxymethyl- β -glucan (sold under the trade name CM Glucan[®] by the company Arnaud) is denoted by K18.

5 In this study, the products (10 mg/ml or 1/100 v/v) are added 30 min before stimulation by IFN- γ + LPS. In none of the cases have these products shown a cytotoxic activity.

10 Table 5A : Production of nitro derivatives (NO₂⁻ in μ M) after stimulation by IFN- γ + LPS +/- 10 mg/ml of the products K17 and K18

Cells	Expt-1	Expt-2	Expt-3	Expt-4
Macrophages	13 (2)*	8 (5)	9 (6)	3 (2)
+K17	5 (2)	2 (1)	7 (1.5)	2 (2)
+K18	6 (1)	4 (1)	5 (1)	1 (2)
Keratinocytes	25 (2)*	28 (5)	19 (6)	13 (2)
+K17	15 (2)	16 (1)	15 (1)	8 (2)
+K18	13 (1)	14 (1)	11 (1)	7 (1)

15 * The values between brackets are those of cells which have not been stimulated by IFN- γ + LPS.

The products K17 and K18 have a high ability to inhibit the production of nitro derivatives by the macrophages and the keratinocytes stimulated by IFN- γ and LPS.

- 20 -

Table 5B : Production of TNF (pg/ml) after stimulation by IFN- γ + LPS +/- or 10 mg/ml of the products K17 and K18

Cells	Expt-1	Expt-2	Expt-3	Expt-4
5 Macrophages	612 (ND)*	920 (155)	903 (55)	700 (ND)
+K17	605 (ND)	902 (95)	970 (45)	695 (ND)
+K18	121 (ND)	320 (125)	512 (20)	333 (ND)
Keratinocytes	205 (ND)	138 (ND)	145 (ND)	108 (ND)
+K17	125 (ND)	98 (95)	100 (ND)	70 (ND)
+K18	130 (ND)	95 (ND)	85 (ND)	82 (ND)

* The values between brackets are those of cells which have not been stimulated by IFN- γ + LPS, ND = non-detectable.

10 The production of TNF- α by the macrophages and the keratinocytes stimulated by IFN- γ + LPS is also detrimentally affected in the presence of the different products in a way comparable with that observed for the nitro derivatives. The products K17 and K18 efficiently
15 inhibit the production of TNF.

2.4. Effect of the products K17 and K18 on the macrophages and the keratinocytes stimulated by IL-4.

20 The cells are stimulated for 48 h in the presence of IL-4 (10 mg/ml), so as to induce the receptor with a low affinity for the IgEs (CD23) at their surface. On completion of this culturing period, 30 to 80% of the keratinocytes and of the macrophages express CD23. The individual variations are in no case the reflection of a
25 different allergic situation between these individuals. Whatever the situation, in this induction phase, none of the tested products modifies this induction of CD23; in fact, a decrease of less than 5% cannot be observed (n=8).

30 After the CD23 has been taken up by IgE-containing immune complexes, the production of a large number of mediators and cytokines (in particular TNF) and

of products resulting from the oxidative metabolism, such as nitrogenous derivatives, is induced. This stimulation redefines in vitro an allergic-type inflammatory reaction.

- 5 Table 6A : Production of nitro derivatives (NO_2^- in μM) after stimulation by IgE-containing immune complexes (IL-4) +/- 10 mg/ml of the products K17 and K18

	Cells	Expt-1	Expt-2	Expt-3	Expt-4
10	Macrophages	15 (5)*	18 (3)	25 (11)	27 (3)
	+K17	16 (3)	17 (6)	19 (7)	30 (6)
	+K18	7 (2)	6 (4)	10 (2)	7 (2)
	Keratinocytes	19 (5)*	22 (1)	13 (1)	7 (1)
	+K17	16 (3)	20 (3)	14 (2)	7 (6)
	+K18	4 (2)	7 (4)	9 (2)	3 (2)

* The values between brackets are those of cells which have not been stimulated by IgE-containing immune complexes.

- 15 The product K18 exhibits an inhibitory activity on the generation of nitro derivatives by the keratinocytes and the macrophages stimulated by IL-4.

Table 6B : Production of TNF (pg/ml) after stimulation by IL-4 +/- K17 and K18

	Cells	Expt-1	Expt-2	Expt-3	Expt-4
20	Macrophages	908 (78)*	135 (40)	508 (45)	712 (58)
	+K17	917 (45)	102 (41)	510 (41)	700 (32)
	+K18	524 (59)	98 (35)	420 (32)	333 (25)
	Keratinocytes	198 (31)*	105 (10)	128 (10)	132 (15)
	+K17	185 (35)	111 (31)	120 (32)	132 (40)
	+K18	95 (23)	60 (35)	25 (12)	35 (12)

* The values between brackets are those of cells which have not been stimulated by IgE-containing immune

complexes, ND = non-detectable.

The product K18 exhibits an inhibitory activity on the generation of TNF by the macrophages and the keratinocytes stimulated by IL-4.

5 It therefore appears that K18 possesses a non-specific and allergic-type anti-inflammatory activity whereas the product K17 only has a non-specific anti-inflammatory activity.

10 Consequently, the effects of the product K18 were evaluated as a function of the dose. The results are illustrated in Figure 1.

K18 therefore inhibits, in a dose-dependent way, the generation of nitro derivatives and also of TNF. The results thus obtained demonstrate that K18 exhibits a
15 generally advantageous anti-inflammatory activity and that this activity is similar to that of H37.

Example 2 : Demonstration of an activity synergy between CM- β -glucan (K18) and ginkgo extract (H37)

20 The anti-inflammatory activities of K18 and H37 and of their combination respectively are determined.

The tests are carried out in a keratinocyte model, as indicated in Example 1 (Materials and Methods) after stimulation, on the one hand, by an IFN- γ + LPS
25 combination and, on the other hand, by IL-4 and IgE-containing immune complexes.

As shown in Figure 2, the products K18 and H37 act in synergy in their anti-inflammatory functions.

It should be recalled that this anti-inflammatory
30 activity covers the non-specific and allergic anti-inflammatory activity.

Example 3 Analysis of the prevention of detrimental cutaneous changes obtained by UV A and UV B irradiation of human skin

35 Organ cultures are produced according to the following protocol: 10 skin fragments from different donors (source : plastic surgery) are placed in inserts which are themselves positioned over culture wells.

Culture medium (antibiotics, FCS) is added to the bottom of the wells, passage between the two compartments being achieved by slow diffusion via a porous membrane (0.45 μm).

5 Before each irradiation, each cosmetic cream (2 mg/cm²) is deposited directly on the skin for 2 hours (control skins without treatment will be analysed in parallel). The 3 creams and the excipient are renewed three times per week on the skins:

- 10 - cream 1: 0.5% CM-glucan
 - cream 2: 0.05% Ginkgo biloba
 - cream 3: CM-glucan + Ginkgo biloba extract (H37)
 - cream 4: excipient (Carbopol placebo)

 After having removed the surplus cream, the skin
15 is then irradiated with 12 J/cm² of UV A and 6 J/cm² of UV B (Vilber Lourmat T40M lamp), equivalent to 20 DEM, doses determined by a preliminary study which make it possible to rapidly obtain lesions at the level of the epidermis and dermis with, in particular, detrimental changes in
20 the collagen and elastic fibres. These doses are, moreover, equivalent to the doses used for the photopatch tests and to the doses used in hairless murine models for generating sunburn cells.

 Irradiation is carried out every other day. Three
25 exposure sessions are carried out and then the skin fragments are collected for the following analyses.

 The production of oxygen derivatives, such as nitric oxide (NO), shows attack by UV radiation.

 The possible protection contributed by the creams
30 will be quantified by evaluating the decrease in the amount of nitrites and the increase in SOD.

1) Quantitative determination of nitric oxide and of nitrites

 Nitric oxide, NO, is an important physiological
35 mediator, not only as vasodilator and neurotransmitter but also as pro-inflammatory agent. Its synthesis is mediated by an enzyme, NO synthase, which is expressed by many cell types and in particular keratinocytes, when

they are activated.

NO, obtained by oxidation of L-arginine by NO synthase, is an unstable product which is rapidly degraded to nitrites (NO_2^-) and nitrates (NO_3^-). It is the spectrophotometric quantitative determination of the nitrites in the culture supernatant in the presence of Griess's reagent which reveals the NO synthase activity.

The results are reported in the table below.

Quantitative determination of the nitrites			
		(nmol/ml)	% of protection
10	Skin treated with cream 1	21.6 \pm 7.3	14.7% \pm 8.2
	Skin treated with cream 2	21.4 \pm 3.6	13.5% \pm 5.8
	Skin treated with cream 3	16.4 \pm 2.9*	33.8% \pm 2.3*
	Skin treated with cream 4	24.9 \pm 5.3	
15	* Statistically significant result (p < 0.05; Student's test)		

The percentage of protection was calculated in the following way: $(A-B/A) \times 100$ where A is the result with cream No. 4 and B the result with cream 1, 2 or 3.

The skins treated with creams 1 and 2 exhibit a slight decrease (not significant) in the production of nitrites. The greatest decrease is obtained with skins treated with cream 3, a difference which is statistically significant with respect to the excipient. Calculation of the percentage of protection confirms these results, cream 3 having in particular a protection of 34%.

2) Quantitative determination of SOD

Attack by U.V. radiation is reflected by a decrease in the level of SOD.

The activity of superoxide dismutase is determined by the technique of McCord and Fridovich. Briefly, superoxide anions are generated by the action of xanthine oxidase on xanthine. The SOD present in the samples can

- 25 -

then inhibit the reduction of cytochrome C by these superoxide anions. The activity of the SOD is related to the amount of reduced cytochrome C remaining in the reaction medium.

5 The results are expressed by percentages of inhibition with respect to the excipient (cream No. 4): the SOD hydrolyses a portion of the free radicals generated by the U.V. attack and the xanthine/xanthine oxidase system. Thus, the decrease in the optical density
10 (proportional to the amount of free radicals) will make it possible directly to quantify the level of SOD.

Quantitative determination of SOD

% of inhibition

	Skin treated with cream 1	11.1% \pm 3.4
	Skin treated with cream 2	7.04% \pm 2.9
15	Skin treated with cream 3	15.1% \pm 3.3*

* Statistically significant result ($p < 0.05$: Student's test)

20 With respect to the excipient, the skins treated with creams 1 and 2 show a slight protection (not significant) against the decrease in the SOD activity induced by UV radiation. This protection is greater with the skins treated with cream 3, a difference which is statistically significant with respect to the excipient.

Conclusion

25 Quantitative determination of the nitrites has demonstrated, for skins treated with cream No. 3, a significant decrease in their amount with respect to the excipient. These results make it possible to envisage the protective activity of cream No. 3 with respect to the
30 detrimental dermal changes generated by inflammatory components. Skins treated with creams 1 and 2 have only a tendency towards protection. There therefore exists a synergy between the components of cream No. 3.

Quantitative determination of SOD seems to confirm this analysis with protection of skins treated with cream No. 3 with respect to detrimental radical changes generated by U.V. radiation. Skins treated with
 5 creams 1 and 2 have only a tendency towards protection, more marked in the case of cream No. 1.

Example 4: Compositions containing combinations according to the invention

A) Formulation with depigmenting agents

10		%
	- Water	70.965
	- Octyl methoxycinnamate	6.000
	- Glyceryl stearate/PEG-100 stearate	5.000
	- Glycerol	5.000
15	- C ₁₂ -C ₁₅ alkyl benzoate	4.000
	- Petrolatum	1.500
	- Cetyl palmitate	1.000
	- Cetyl alcohol	1.000
	- Stearyl alcohol	0.500
20	- Sodium sulphite	0.025
	- Sodium disulphite	0.025
	- Hydroquinone	2.000
	- Citric acid	0.15
	- Carbomer	0.300
25	- Tocopheryl acetate	0.100
	- Phenoxyethanol	0.730
	- Methylparaben	0.200
	- Propylparaben	0.070
	- Sodium hydroxide	0.135
30	- Disodium EDTA	0.200
	- β -Glucan	1.0
	- Ginkgo biloba extract	0.1

B) Formulation with retinol

		%
35	- Water	56.42
	- Cetearyl octanoate	9.00
	- Octyl methoxycinnamate	8.00

- 27 -

	- Lactose	5.00
	- Glycerol	5.00
	- Hydrogenated groundnut oil	5.00
	- Glyceryl polymethacrylate	3.45
5	- Butylmethoxydibenzoylmethane	1.50
	- Isopropyl myristate	1.00
	- Hydrogenated lecithin	1.00
	- β -Glucan	1.00
	- Ammonium hydroxide	0.75
10	- Phenoxyethanol	0.73
	- C ₁₀ -C ₃₀ Alkyl acrylate copolymer/acrylates	0.50
	- Poloxamer 407	0.50
	- Tocopheryl acetate	0.50
	- Methylparaben	0.20
15	- Ginkgo biloba extract	0.10
	- Carbomer	0.10
	- BHT	0.10
	- Propylparaben	0.07
	- Propylene glycol	0.05
20	- Retinol	0.03
		100.00

C) Formulation with retinol

		%
	- Water	69.689
25	- Octyl hydroxystearate	6.2942
	- Glycerol	4.0000
	- Ceteareth-20/stearyl alcohol	3.0000
	- Ceteareth-20/cetearyl alcohol	3.0000
	- Glyceryl distearate	2.8000
30	- Dimethicone	2.5000
	- C ₁₂ -C ₁₅ Alkyl lactate	1.5000
	- Steareth-10	1.4000
	- Cholesterol	1.0000
	- Acetylated lanolin alcohol/cetyl acetate	1.0000
35	- Polysorbate 80	0.7000
	- Sodium citrate	0.5160
	- C ₁₃ -C ₁₄ Isoparaffin/laureth-7	0.5000
	- Stearyl alcohol	0.5000
	- Polysorbate 20/retinol	0.1058

	- BHT	0.1000
	- Methylparaben	0.2000
	- Fragrance	0.0500
	- Propylparaben	0.0300
5	- Citric acid	0.0150
	- Ginkgo biloba extract	0.1
	- Panthenol	1.0
		<hr/>
		100.-
10	D) Formulation with tretinoin	
	- Tretinoin	0.05 g
	- β -Glucan	0.50 g
	- Ginkgo biloba extract	0.10 g
	- Light liquid paraffin	25.00 g
15	- Non-crystallizable 70 per cent sorbitol solution	5.00 g
	- Hydroxyoctacosanyl hydroxystearate	5.00 g
	- Methoxymacrogol 22/dodecyl glycol copolymer	5.00 g
20	- Macrogol 45/dodecyl glycol copolymer	3.00 g
	- Stearoxytrimethylsilane and stearyl alcohol	1.00 g
	- Dimethicone	1.00 g
	- Fragrance	0.25 g
25	- Methyl para-hydroxybenzoate	0.20 g
	- Sodium edotato	0.10 g
	- Quaternium 15	0.10 g
	- Butylated hydroxytoluene	0.10 g
	- Citric acid monohydrate	0.10 g
30	- Purified water	53.495 g

CLAIMS

1. Use of at least two compounds chosen from components having an a) anti-radical, b) anti-inflammatory and c) anti-allergic activity for the preparation of a composition exhibiting at least two of the a), b) and c) activities intended for the treatment of sensitive and/or allergic skin.
2. Use according to Claim 1, characterized in that the a), b) and c) activities are exerted in the composition.
3. Use according to either of Claims 1 and 2, characterized in that the component or components exhibiting an anti-radical activity are chosen from free-radical scavengers, anti-lipoperoxidants and stimulants of the endogenous production of the enzymes which degrade free radicals.
4. Use according to one of Claims 1 to 3, characterized in that the components exhibiting an anti-inflammatory activity are chosen from prostaglandin inhibitors, inhibitors of cytokine production and inhibitors of leukotriene production.
5. Use according to one of Claims 1 to 4, characterized in that the anti-allergic components are chosen from inhibitors of lymphocyte proliferation, inhibitors of the internalization of HLA receptors and inhibitors of cytokine production.
6. Use according to one of Claims 1 to 5, characterized in that the composition inhibits the synthesis or the expression of neuromediators by cutaneous cells.
7. Use according to one of Claims 1 to 6, characterized in that at least one component is chosen from the following group: Ginkgo biloba and its extracts, iramine, D-panthenol, β -sitosterol, modulene, α -tocopherol and its derivatives, α -tocopherol phosphate, β -glucan and its derivatives, eicosapentanoic acid, 18β -glycyrrhetinic acid, glycyrrhetinic acid monoglucuronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C, glutathione, epidermal thymus

factor, imidazole derivatives, triazole derivatives and lipacid,

and with the condition that the combination vitamin E and Scutellaria extract is excluded.

5 8. Use according to Claim 7, characterized in that at least two components are chosen from the following group: Ginkgo biloba and its extracts, iramine, D-panth-enol, β -sitosterol, modulene, α -tocopherol and its derivatives, α -tocopherol phosphate, β -glucan and its
10 derivatives, eicosapentanoic acid, 18β -glycyrrhetic acid, glycyrrhetic acid monoglucuronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C, glutathione, epidermal thymus factor, imidazole derivatives, triazole derivatives and
15 lipacid,

and with the condition that the combination vitamin E and Scutellaria extract is excluded.

9. Use of at least two compounds according to one of Claims 1 to 8 for the preparation of a medicament
20 intended for the treatment of a complaint chosen from atopy, psoriasis, erythema multiforme, xerodermatitides, systemic lupus erythematosus, pemphigus, dermatitides, rosacea, neurodermatitides and alopecia.

10. Use according to one of Claims 1 to 9, character-
25 ized in that the composition contains at least one of the following combinations: α -tocopherol/Ginkgo biloba extract, carboxymethyl- β -glucan/Ginkgo biloba extract, β -sitosterol/D-panthenol, modulene/lactoferrin and panth-enol/green tea extract.

30 11. Method for the cosmetic treatment of sensitive skin, characterized in that a dermocosmetic composition which contains a synergic combination of at least two components chosen from

- a) anti-radicals,
35 b) anti-inflammatories,
c) anti-allergics,

is applied on the region concerned, the said components being chosen so that the final composition exhibits at least two of the a), b) and/or c) activities.

12. Process for the preparation of a composition with hypoallergenic or immunomodulatory activity and/or which is intended for the treatment of sensitive skin, characterized in that it comprises the stages during which

- 5 a) components are selected which exhibit at least one anti-inflammatory, anti-radical and/or anti-allergic activity, at least two components exhibiting at least two different activities are then combined and it is determined if at least one of the activities
10 is potentiated by the combination of these two components,
- b) the combinations exhibiting at least two of the activities chosen from the anti-inflammatory, anti-radical and anti-allergic activities, and in which
15 at least one of the activities is potentiated, are selected,
- c) at least one of the selected combinations is mixed with dermatologically or cosmetologically acceptable excipients, in order to obtain the composition.

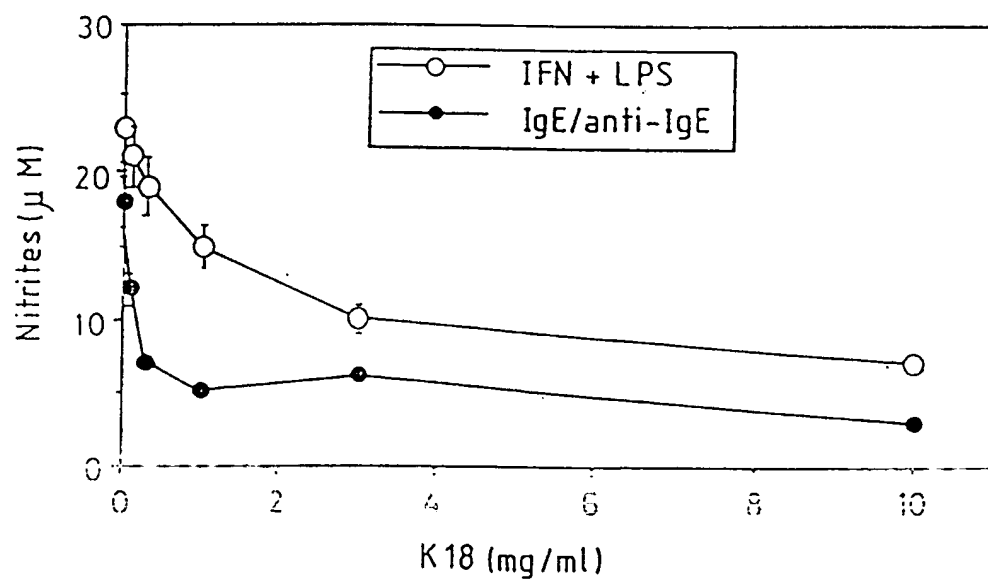
20 13. Composition capable of being obtained by the process according to Claim 12, characterized in that it contains at least one, preferably at least two, components chosen from the group consisting of Ginkgo biloba and its extracts, iramine, D-panthenol, modulene,
25 α -tocopherol and its derivatives, β -glucan and its derivatives, eicosapentanoic acid, 18β -glycyrrhetic acid, glycyrrhetic acid monoglucuronide, stearyl glycyrrhetinate, Scutellaria extract, lactoferrin, green tea extract, vitamin C, glutathione, epidermal thymus
30 factor,azole derivatives and lipacid,
and with the condition that the combination vitamin E and Scutellaria extract is excluded.

14. Composition according to Claim 13, characterized in that it contains a synergic combination of a Ginkgo
35 biloba extract and of β -glucan or of one of its derivatives.

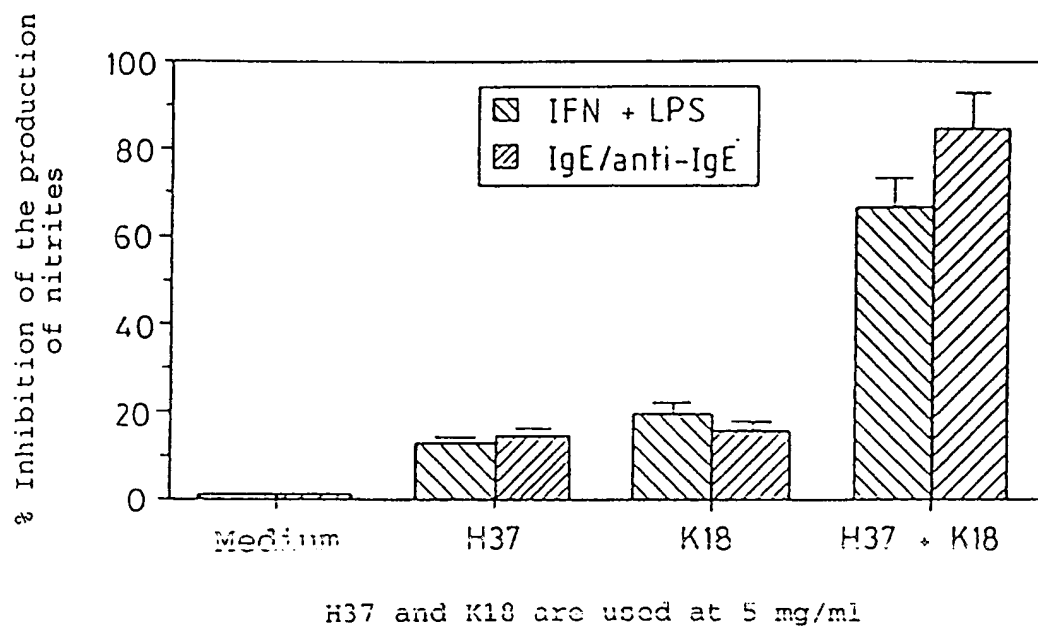
15. Composition according to either of Claims 13 and 14, characterized in that the β -glucan is substituted by carboxymethyl groups.

16. Composition according to one of Claims 13 to 15, characterized in that the terpene concentration in the Ginkgo biloba extract is less than 1% w/w of dry matter.
17. Composition according to one of Claims 13 to 16,
5 characterized in that the concentration of Ginkgo biloba extract is between 0.001% and 10% w/w.
18. Composition according to one of Claims 13 to 17, characterized in that the β -glucan concentration is between 0.001% and 10% w/w.
- 10 19. Composition according to Claim 13, characterized in that it contains a combination chosen from drieline + lactoferrin, panthenol + green tea extract or D-panthenol + β -sitosterol.
20. Composition according to one of Claims 13 to 19,
15 characterized in that it additionally contains at least one other active principle which is active by the cutaneous topical route.
21. Composition according to Claim 20, characterized in that it contains at least one active principle chosen
20 from the group of retinoids and depigmenting agents.

1/2

FIG_1

2/2

FIG_2

INTERNATIONAL SEARCH REPORT

Intern. Pat. Application No.
PCT/IB 97/01318

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 11189 A (LVMH RECHERCHE) 8 August 1991 see claims 1,4,5,7,9 see page 3, line 9-17 see page 5, line 19-23 ---	1-3,7,8, 11
X	EP 0 332 478 A (LVMH RECHERCHE) 13 September 1989 see page 1 see page 3, line 20-24 see example 13 ---	1,7
X	DE 296 07 273 U (M.BRAUN) 1 August 1996 see claim 1 see page 1 -----	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

9 February 1998

Date of mailing of the international search report

16/02/1998

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/IB 97/01318

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